

### SUPPORT FOR THE AMENDMENT

The claims have been amended to be placed in proper form and to include a proviso as suggested by the Examiner. Support for the above amendment and the newly added claims is found at page 9, lines 1-3, and page 10, line 33, to page 11, line 25, of the specification. No new matter is believed to be introduced by the above amendment.

### REMARKS

Claims 1-4, 6-12, and 14-21 are pending. Favorable reconsideration is respectfully requested.

At the outset, Applicants thank Examiner Gerstl for the courteous and helpful discussion of the present application held on September 4, 2002, and the telephone discussion held October 30, 2002. Further, Applicants thank Examiner Gerstl for helpful suggestions and for indicating that the above amendment would place the claims in condition for allowance.

The rejection of Claims 1-4, 6-8, 10, 14, and 16 under 35 U.S.C. § 102(b) over Islip is obviated by the above amendment. Further, Islip fails to disclose or suggest the claimed compounds and methods in light of the following remarks.

Islip merely discloses that a 2-ureido-1,3-thiazole derivative of formula (I) may be substituted so that R is either bromine or iodine when R<sub>1</sub> is a C<sub>1</sub>-C<sub>6</sub> alkyl having carbonyl group bound to the ureido group (see compounds 1-5 in Table 1 at page 102).

In direct contrast, the claimed derivatives of formula (I) **cannot** contain R<sub>1</sub> that is a C<sub>1</sub>-C<sub>6</sub> alkyl having 1-6 oxo groups when R is a bromine or iodine atom (See amended Claim 1 above). The Examiner recognized during the above-mentioned discussions that such

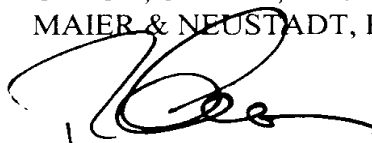
compounds exclude the compounds disclosed by Islip. In accordance with the Examiner's suggestion, Applicants have amended the claims so that Islip clearly fails to disclose or suggest the claimed invention. Accordingly, withdrawal of this ground of rejection is respectfully requested

The rejection of Claims 1-4 and 17 under 35 U.S.C. § 101 is believed to be obviated by the above amendment. Claims 1-4 and 17 have been amended so that they are placed in proper form. More specifically, Claims 1-4 and 17 are amended to include process steps. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants respectfully submit that the present application is now in condition for allowance. Favorable reconsideration is respectfully requested. Should anything further be required to place the application in condition for allowance, the Examiner is requested to contact the undersigned by telephone.

Respectfully submitted,

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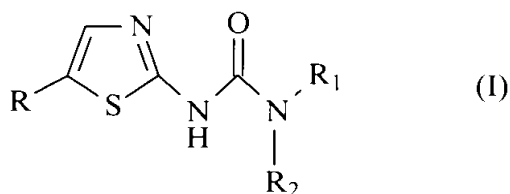
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Serial No: 09/830,668  
Amendment Filed on:  
HEREWITH

IN THE CLAIMS

Please amend the claims as shown on the attached pages.

--1. (Amended) [The use of a compound which is] A method of treating, arresting, alleviating, or reducing cell proliferative disorders associated with an altered cell dependent kinase activity in a patient comprising administering a 2-ureido-1,3-thiazole [derivatives] derivative of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;
- ii.) C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R<sub>1</sub> is an optionally further substituted group selected from:

- i) straight or branched C<sub>1</sub>-C<sub>6</sub>;
- ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
- iii) aryl or arylcarbonyl;
- iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched

alkyl chain, with the proviso that R<sub>1</sub> is not a C<sub>1</sub>-C<sub>6</sub> alkyl having 1-6 oxo groups when R is a bromine or iodine atom;

R<sub>2</sub> is hydrogen, a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R<sub>1</sub> and R<sub>2</sub> form a substituted or unsubstituted group selected from:

- i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or
- ii) a 9 to 11 membered spiro-heterocyclic compound;

or a pharmaceutically acceptable salt thereof to the patient [; in the manufacture of a medicament for treating cell proliferative disorders associated with an altered cell dependent kinase activity].

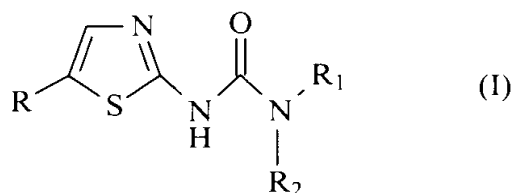
2. (Amended) [Use] The method according to [claim 1] Claim 1, wherein the [said] cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative disorders.

3. (Amended) [Use] The method according to [claim 2] Claim 1, wherein the [cancer] cell proliferative disorder is selected from the group consisting of a carcinoma, squamous cell

carcinoma, hematopoietic [tumors] tumor of myeloid lineage, [or] hematopoietic tumor lymphoid lineage, [tumors] tumor of mesenchymal origin, [tumors] tumor of the central nervous system, [and] tumor of the peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoctanthoma, thyroid follicular [cancer] cancer, and Kaposi's sarcoma.

4. (Amended) [Use] The method according to [claim 1] Claim 1, wherein the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

6. (Amended) A [compound which is a] 2-ureido-1,3-thiazole derivative of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;
- ii) C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

$R_1$  is an optionally further substituted group selected from:

- i) straight or branched  $C_1$ - $C_6$  alkyl;
- ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
- iii) aryl or arylcarbonyl;
- iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched

alkyl chain, with the proviso that  $R_1$  is not a  $C_1$ - $C_6$  alkyl having 1-6 oxo groups when R is a bromine or iodine atom;

$R_2$  is hydrogen, a straight or branched  $C_1$ - $C_4$  alkyl or  $C_2$ - $C_4$  alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

$R_1$  and  $R_2$  form a substituted or unsubstituted group selected from:

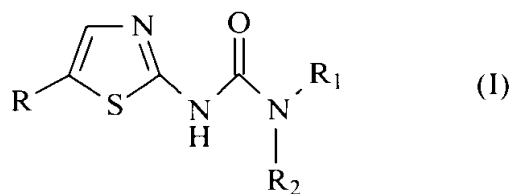
- i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or
- ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically

acceptable salt thereof; [for use as a medicament]; provided that:

- a) when R is a chlorine atom and  $R_2$  is hydrogen, then  $R_1$  is not methyl, phenyl or trifluoromethylphenyl; and
- b) when R is methyl and  $R_2$  is hydrogen, then  $R_1$  is not 4- (5-oxazolyl)phenyl.

7. (Amended) A [compound which is a] 2-amino-1,3-thiazole derivative of formula

(I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;
- ii) C<sub>3</sub>-C<sub>6</sub> cycloalkyl ;
- iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or

branched alkyl chain;

R<sub>1</sub> is an optionally further substituted group selected from:

- i) straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;
- ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
- iii) aryl or arylcarbonyl;
- iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched

alkyl chain, with the proviso that R<sub>1</sub> is not a C<sub>1</sub>-C<sub>6</sub> alkyl having 1-6 oxo groups when R is a bromine or iodine atom;

R<sub>2</sub> is hydrogen, a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R<sub>1</sub> and R<sub>2</sub> form a substituted or unsubstituted group selected from:

- i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof; provided that:

- a) when R is chlorine or bromine and R<sub>2</sub> is hydrogen, then R<sub>1</sub> is not unsubstituted C<sub>1</sub>-C<sub>3</sub> alkyl, phenyl, trifluoromethylphenyl or an optionally substituted phenylcarbonyl;
- b) when R is methyl and R<sub>2</sub> is hydrogen, then R<sub>1</sub> is not methyl, phenyl or 4-(5-oxazolyl)phenyl;
- c) when R is nitrophenyl and R<sub>2</sub> is hydrogen, then R<sub>1</sub> is not haloalkyl;
- d) when R is bromine or chlorine, then R<sub>1</sub> and R<sub>2</sub> are not both methyl groups.

8. (Amended) [A] The derivative [compound of formula (I)] according to [claim 7] Claim 7, wherein R is a halogen atom, a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl group, a phenyl group, [or] a cycloalkyl group; R<sub>2</sub> is hydrogen and R<sub>1</sub> is an optionally substituted group selected from alkyl, aryl or arylalkyl; with the proviso that R<sub>1</sub> is not a C<sub>1</sub>-C<sub>6</sub> alkyl having 1-6 oxo groups when R is a bromine or iodine atom.

9. (Amended) [A] The derivative [compound of formula (I)] according to [claim 8] Claim 8, wherein R is [bromine or] bromine, chlorine, a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl group, a phenyl group, [or] a cycloalkyl group; R<sub>2</sub> is hydrogen and R<sub>1</sub> is an optionally substituted aryl or an arylalkyl or heterocyclyl-alkyl group [with] having from 1 to 4 carbon atoms within the alkyl chain.

10. (Amended) [A] The derivative [compound of formula (I)] according to [claim 7] Claim 7, wherein

R is a halogen atom or is selected from the group consisting of nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy, and aryl each optionally substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4- morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy, or R is an aryl group optionally substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulphonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy;

R<sub>1</sub> is a straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl group or an aryl group, each optionally substituted as above reported for R, with the proviso that R<sub>1</sub> is not a C<sub>1</sub>-C<sub>6</sub> alkyl having 1-6 oxo groups when R is a bromine or iodine atom;

R<sub>2</sub> is a hydrogen atom; and pharmaceutically acceptable salts thereof; provided that:

- a) when R is chlorine or bromine then R<sub>1</sub> is not unsubstituted C<sub>1</sub>-C<sub>3</sub> alkyl, phenyl, trifluoromethylphenyl or an optionally substituted phenylcarbonyl;
- b) when R is methyl then R<sub>1</sub> is not methyl, phenyl or 4-(5oxazolyl)phenyl;
- c) when R is nitrophenyl then R<sub>1</sub> is not haloalkyl.

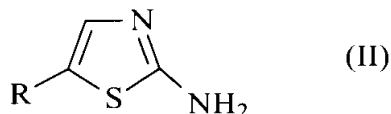
11. (Amended) [A] The derivative [compound of formula (I)] according to [claim 7] Claim 7, wherein R is a straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl group and, together with the nitrogen atom to which they are bonded, R<sub>1</sub> and R<sub>2</sub> form a substituted or unsubstituted,

optionally benzocondensed or bridged 5 to 7 membered heterocycle, or a 9 to 11 membered spiro-heterocycle.

12. (Amended) [A] The derivative [compound of formula (I)] according to [ claim 7] Claim 7, wherein R is a straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl group; R<sub>2</sub> is a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl or alkynyl group and R<sub>1</sub> is an aryl or arylalkyl group with from 1 to 4 carbon atoms within the straight or branched alkyl chain.

14. (Amended) A process for preparing [a compound] the derivative according to [of formula (I), as defined in claim] Claim 7, [which process comprises] comprising:

a) [when R<sub>2</sub> is a hydrogen atom] reacting a compound of formula (II) when R<sub>2</sub> is a hydrogen atom

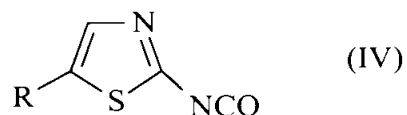


[wherein R is as defined in claim 7,] with a compound of formula (III) wherein R is as defined in claim 7

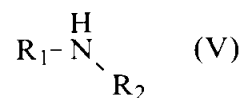


wherein R<sub>1</sub> is as defined in claim 7; or

b) [when R<sub>2</sub> is as defined in claim 7] reacting a compound of formula (IV) when R<sub>2</sub> is as defined in claim 7

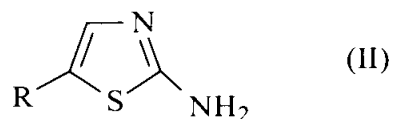


[wherein R is as defined in claim 7,] with a compound of formula (V) wherein R is as defined in claim 7



wherein R<sub>1</sub> and R<sub>2</sub> are as defined in claim 7; and[, if desired,] optionally  
 converting a 2-ureido-1,3-thiazole derivative of formula (I) into another such  
 derivative of formula (I), [and/or into] a salt thereof, or a mixture thereof.

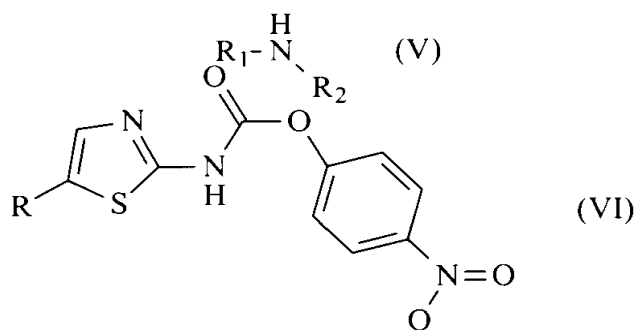
15. (Amended) A process for preparing [a compound of formula (I), as defined in  
 claim 7] the derivative according to Claim 7, [which process comprises] comprising  
 reacting a compound of formula (II)



wherein R is as defined in claim 7, with 4-nitrophenylchloroformate, or a polymer supported form of it, thus obtaining a compound of formula (VI), or a polymer supported form of it,

wherein R is as defined in claim 7; and

reacting a compound of formula (VI) with a compound of formula (V)

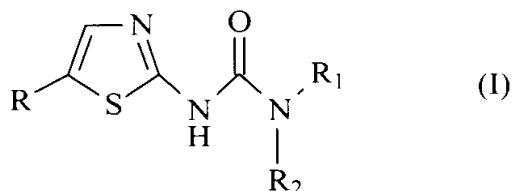


wherein R<sub>1</sub> and R<sub>2</sub> are as defined in claim 7; and[, if desired] optionally,

converting a 2-ureido-1,3-thiazole derivative of formula (I), or a polymer supported form of it, into another such derivative of formula (I), [and/or into] a salt thereof or a mixture thereof.

16. (Amended) A pharmaceutical [composition] composition, comprising at least one [or more] pharmaceutically acceptable [carriers] carrier or diluent [and/or diluents] and[, as the active principle, an effective amount of a compound] the derivative of formula (I) [as defined in claim 1] according to Claim 1.

17. (Amended) [Use according to claim 1 wherein the medicament enables] A method of treating, arresting, alleviating, or reducing tumor angiogenesis and metastasis inhibition in a patient, comprising administering a 2-ureido-1,3-thiazole derivative of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;
- ii.) C<sub>3</sub>-C<sub>6</sub> cycloalkyl;
- iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or

branched alkyl chain;

R<sub>1</sub> is an optionally further substituted group selected from:

- i) straight or branched C<sub>1</sub>-C<sub>6</sub>;
- ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
- iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched

alkyl chain, with the proviso that R<sub>1</sub> is not a C<sub>1</sub>-C<sub>6</sub> alkyl having 1-6 oxo groups when R is a bromine or iodine atom;

R<sub>2</sub> is hydrogen, a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R<sub>1</sub> and R<sub>2</sub> form a substituted or unsubstituted group selected from:

- i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or
- ii) a 9 to 11 membered spiro-heterocyclic compound;

or a pharmaceutically acceptable salt thereof to the patient.--

--Claims 19-21 are new.--